

# Bipolar Disorder: Alternatives to Lithium

by Jerry Cott, PhD

## Bipolar Disorder: Definition, Incidence, and Diagnosis

Bipolar disorder (BP), also known as manic-depressive illness, is a common, recurrent, and severe psychiatric disorder that causes major shifts in a person's mood, energy, and ability to function. The mood swings of BP are dramatic - ranging from euphoric and/or irritable to sad and hopeless, and then back again, often with periods of normal mood between episodes. From 25% to 50% of patients with BP attempt suicide at least once (Jamison, 2000).

From two to ten million American adults, (one to five percent of the population) have BP, depending on how it is defined (Keck et al., 2001; Hirschfeld, 2001; Akiskal et al., 2000). The higher estimates include many with the so-called bipolar spectrum disorder. BP typically develops in late adolescence or early adulthood and it is more likely to affect the children of parents who have the illness. Symptoms often go unrecognized, resulting in many years of suffering before it is diagnosed and treated. Drug abuse, for example, is often seen in youth and in adults with BP and it can be unclear which leads to which. People with the dual diagnosis of drug abuse and bipolar disorder may be more difficult to manage.

Severe episodes of mania or depression may include psychotic symptoms, such as hallucinations and delusions. People with BP who have these symptoms are often incorrectly diagnosed with schizophrenia.

BP cannot be identified physiologically. The diagnosis of BP is made on the basis of symptoms, their course, and family history. Episodes of mania and depression typically recur across the life span. Between episodes most people with BP are free of symptoms, though most suffer from medication side effects, and at least one-third have residual symptoms. While people with BP can often lead productive lives, the natural course of BP tends to worsen, such that episodes may become more frequent or more severe than those experienced when the

symptoms first appeared (Goodwin and Jamison, 1990).

BP in children is a condition that has only recently been recognized as a legitimate diagnosis. It is underrecognized for many reasons including lack of awareness, diagnostic confusion, and the different presenting clinical picture in children. Available data strongly suggests that prepubertal childhood BP is a non-episodic, chronic, rapid cycling, mixed manic state. It may be comorbid with attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) or it may demonstrate features of ADHD and CD, further complicating recognition and subsequent treatment (Mohr, 2001). Children with mania are more likely to be irritable and prone to destructive tantrums than to be overly happy. Mixed symptoms also are common in youths with BP, while older adolescents may have more classic episodes and symptoms.

## Conventional Treatment: Lithium and Anticonvulsants

Medications known as "mood stabilizers", including lithium and anticonvulsant drugs, are usually prescribed to help control BP symptoms (Sachs et al., 2000), and this treatment may be life-long. Other medications (such as antipsychotics or antidepressants) are added for shorter periods, to treat episodes of mania or depression that break through despite the mood stabilizer. Unfortunately, these add-on medications are often left in place for extended periods of time without reassessing medical need.

Lithium is a toxic metal that has been used, not without controversy, in psychiatry since 1949. It was approved for use in BP in 1970. The delay was due primarily to concerns about its acute toxicity symptoms of which include nausea, vomiting, diarrhea, coarse tremor, ataxia, coma, and convulsions. It was shown that the worst of these effects could be avoided by regularly monitoring plasma levels to assure that they stay



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within a certain range. Unfortunately, lithium is ineffective or not tolerated by many patients, and sustained chronic use may cause irreversible nephrotoxicity and thyroid dysfunction over long-term use, though it remains the "gold standard" for acute treatment (Poolsup et al., 2000).

Lithium was followed by approval of the anti-convulsant medication, valproate, in 1995. Valproate is increasingly used for the management of acute mania. However, weight gain and hyperandrogenism in valproate-treated women with seizure disorder (Isojarvi et al., 1993) suggesting problems with maintenance therapy in female patients, particularly adolescents (Piontek and Wisner, 2000). There is some evidence that valproate may lead to adverse hormonal changes in teenage girls and to polycystic ovary syndrome in women who began taking the medication before age 20 (Isojarvi et al., 1993; O'Donovan et al., 2002). Anticonvulsant drugs such as carbamazepine have been found effective in many patients and are routinely used. Others anticonvulsants are also used in acute mania though none have been approved for this use. For carbamazepine, there are also concerns about neutropenia and interactions with other drugs. These anticonvulsants are often combined with lithium, or with each other, in an effort to increase their effect.

The only drugs to be approved for BP (lithium and valproate) have only been shown to be effective in acute mania. The vast majority of the life of people with BP is spent as either normal or mildly depressed. Commercial drugs are not tested for their usefulness in continuation or maintenance treatment (ability to prevent relapse) of BP. Rather, drugs shown to be effective acutely are used indefinitely. This is a serious flaw in the drug approval process. A recent study showed that both lithium and valproate did not differentiate from placebo in prevention of recurrence of BP episodes (Bowden et al., 2000). During the depressive phase of bipolar illness, standard antidepressant drugs are generally used. While they may appear to work, they often cause additional problems including rapid cycling between extreme irritability and depression.

Women with BP who wish to conceive, or who

become pregnant, face special challenges since lithium, valproate, and carbamazepine are all considered potentially teratogenic (Cohen et al., 1994; Jones et al., 1989; Robert and Guiband, 1982). Lithium use has been associated with Ebstein's anomaly, poor respiratory effort and cyanosis, rhythm disturbances, nephrogenic diabetes insipidus, thyroid dysfunction, hypoglycemia, hypotonia and lethargy, and hyperbilirubinemia (Pinelli et al., 2002). Valproate is teratogenic, highly concentrated in the fetus, and is contraindicated in pregnancy (as are thalidomide and diethylstilbestrol). Carbamazepine results in mild skeletal anomalies in rats and has been implicated in human congenital malformations including spina bifida, digital malformations and craniofacial defects (Jones et al., 1989). Haloperidol, a neuroleptic often used for treatment of mania, has been implicated in birth defects in humans (McCullar and Heggeness, 1975; Hanson and Oakley, 1975). Less toxic maintenance treatments for BP are desperately needed.

### **An Alternative Drug: Verapamil**

Reports of the mood stabilizing effects of calcium channel blockers (CCBs) for BP have been reported for two decades (Dubovsky et al., 1982). In general medical practice, CCBs are used to treat states related of cellular hyperexcitability such as cardiac arrhythmia, angina, hypertension and premature labor (Dubovsky et al., 1986). The long-term safety record of the oldest CCB, verapamil, is favorable (Opie et al., 2000). While several CCBs have been tried in BP, verapamil has been the most studied and the literature includes controlled double-blind studies of both acute mania and maintenance (reviewed by Dubovsky, 1993; Dubovsky and Buzan, 1997).

There are at least 9 controlled reports of verapamil treatment of mania (Table 1). These included a total of 99 subjects who received verapamil. Of the five parallel controlled studies, four used active controls. Giannini et al. (1985) reported verapamil superior to clonidine. Hoschl and Kozeny (1989) found verapamil comparable to lithium and to a combination of lithium and neuroleptic. Garza-Trevino et al. (1992) found verapamil comparable to lithium, but Walton et al. (1996) found lithium superior. The placebo-controlled trial from Janicak et al.

**Table 1. Controlled Double-Blind Studies of Verapamil in Acute Mania**

	Design	Control	N on VER	Results
Dubovsky et al., 1982	A-B-A	PI	1	1/1 respond to VER
Giannini et al., 1984	A-B-A	PI and Li	12	VER > PI
Giannini et al., 1985	parallel	clonidine	10	VER > clonidine
Dubovsky et al., 1986	crossover	PI	7	5/7 respond to VER
Dose et al., 1986	A-B-A	PI	8	5/8 respond to VER
Haskell and Kozeny 1989	parallel	Li, Li+NL	12	VER = NL = Li+NL
Garza-Trevino et al., 1992	parallel	Li	12	VER = Li
Walton et al., 1996	parallel	Li	20	Li > VER
Janicak et al., 1998	parallel	PI	17	VER = PI

Li= lithium; NL=neuroleptic; VER=verapamil; PI=placebo

(1998) found no effect from verapamil. Because of different designs, severity of subjects entering the studies, outcome measures, and use of rescue medications, these reports are not suitable for a meta-analysis but are displayed below.

In addition to the controlled clinical trials, Wisner et al. (2002) described their experience with verapamil in 28 outpatient women (some pregnant) during an acute BP episode. Of the women with depression and mania, 39% and 100% responded, respectively. Seven of the nine patients with mixed states responded. Six of eight patients who received continuation therapy remained well. These data provide evidence that verapamil is effective for mania and that the response rate compares favorably to that of other mood stabilizers (Wisner et al., 2002).

A recent report suggests that magnesium may augment the mood stabilizing effects of verapamil (Giannini et al., 2000). The authors compared the antimanic effects of a verapamil-magnesium oxide (V-M) combination with a verapamil-placebo combination (V-P) in patients pretreated with verapamil. The V-M combination was found to be significantly more

effective than V-P in reducing manic symptoms ( $P=0.015$ ). The authors suggest that magnesium may have clinical application as an adjunct to verapamil in the maintenance therapy of mania (Giannini et al., 2000). While magnesium is known to compete with calcium on the cellular level, it is not known if this is related to the therapeutic effect.

#### **Now the Fishy Part: Omega-3 Fatty Acids**

The human diet includes several different types of fats. In western societies, most people eat more solid fats rich in saturated fatty acids and less soft fats rich in polyunsaturated fatty acids than they did a century or two ago. In addition, people now eat a different type of polyunsaturated fats. Today, the average diet contains an excess of corn, soy or other plant food oils rich in omega-6 fatty acids, but low in the fats from plants such as flax, and fish that are so rich in omega-3 fatty acids. Interestingly, a vegetarian diet may exacerbate this problem (Sanders, 1999). Nearly 20 years ago, Bang et al. (1976) suggested that the low mortality rate from coronary heart disease among Greenland Eskimos might be due to their high consumption

of seafood. Since then other observational, case-control and intervention studies have also suggested that eating a diet rich in the essential omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), affords protection against heart disease.

The human brain and the retina of the eye consist largely of fatty tissue characterized by long-chain polyunsaturates. In addition to providing energy, the fatty acids in our diet provide critical building blocks for the brain and the retina of the eye. To optimize the development of the fetus and the infant, it is important to ensure a sufficient intake of omega-3 fatty acids, especially during the last trimester of pregnancy and the first six months after birth. To accomplish this, most mothers-to-be need to include omega-3 fatty acids in their diet during their pregnancy and breastfeeding period. Children born at term demonstrate a difference in mental development between those who get sufficient omega-3 fatty acids from breast milk or fortified infant formula, and those who received non-fortified infant formula based solely on vegetable oils which are rich in omega-6 fatty acids, but low in omega-3 fatty acids. It has convincingly been proven that children who are born at term and get sufficient amounts of omega-3 fatty acids tend to have a better intellectual capacity than children who receive standard infant formulae (Willatts et al., 1998; Birch et al., 2000). The explanation for these results given by the researchers is that omega-3 fatty acids, are absorbed into brain cells during the later stage of pregnancy and the first period after birth, and that they are a prerequisite for normal brain development.

Neuronal membranes contain high concentrations of DHA as well as arachidonic acid (AA); both of these essential fatty acids are crucial components of the phospholipid bilayer (each comprises approximately 25% of the phospholipid content) (Mahadik and Evans, 1997). DHA is selectively concentrated in synaptic membranes where it has a crucial role in maintaining the biophysical properties determining 3-dimensional receptor conformation (Mitchell et al., 1998). Depletion of omega-3 fatty acids, particularly DHA, impairs membrane function and may also be of etiological importance in depression, aggression, schizophrenia and other mental and neurological

disorders (Hibbeln et al., 1989; Hibbeln and Salem, 1995; Hillbrand et al., 1997; Hibbeln et al., 1997; Cott, 1999).

### **Omega-3 and Mood**

It has been theorized that adequate long-chain polyunsaturated fatty acids, particularly DHA, may reduce the development of depression just as they may reduce coronary artery disease (Hibbeln and Salem, 1995; Horrocks and Yeo, 1999). There appears to be an inverse relationship between the prevalence of major depression and the amount of fish consumed per capita worldwide (Hibbeln, 1998). Patients with major depression have an increased ratio of AA to EPA in their plasma (Maes et al., 1996; Adams et al., 1996) and erythrocytes (Maes et al., 1996; Edwards et al., 1998; Adams et al., 1996). Fatty acid composition of phospholipid in erythrocyte membranes (thought to mirror neuronal membranes) of depressive patients showed significant depletions of total omega-3 PUFA, particularly DHA (Peet et al., 1998).

In a sample of 3,204 Finnish adults, depressive symptoms were estimated with the Beck Depression Inventory and a frequency question was used to approximate omega-3 fatty acid intake as measured by fish consumption. Multiple logistic regression analysis was conducted to assess the association between depression and fish consumption. After the analysis was adjusted for potential confounding factors, the likelihood of having depressive symptoms was significantly higher among infrequent fish consumers than among frequent consumers (Tanskanen et al., 2001).

### **Omega-3 and Pregnancy, Breast-feeding and Postpartum Depression**

Breast milk, unlike infant formula, has relatively high concentrations of DHA and EPA (Salem, 1989). The World Health Organization recommends that DHA and EPA be added to infant formulas. European infant formulas are routinely fortified with these fatty acids, but until June 2001, the FDA had not allowed the addition of either DHA or EPA to infant formulas sold in the United States. These omega-3 fatty acids are crucial in the development of the fetal and neonatal brain and nervous system (Holman et al., 1991). Intellectual development may also suffer in infants deprived of these fatty acids. Recent studies have found that infants whose

formula was supplemented with long chain PUFAs during their first months of life performed better at both 10 months and 18 months of age on a problem-solving test than infants given the standard unsupplemented formula (Willatts et al., 1998; Birch et al., 2000). Depletion of maternal omega-3 fatty acids has been noted during pregnancy (Otto et al., 1997). The physiology of pregnancy involves the mobilization of polyunsaturated fatty acids from maternal stores to the fetus, and supplementation with essential fatty acids may ensure adequate supplies for the needs of the mother and the developing fetus (Holman et al., 1991; Al et al., 1995). Hornstra et al. (1995) demonstrated that maternal essential fatty acids, especially DHA, progressively decrease during pregnancy. These decreased levels of DHA in plasma and erythrocytes may remain low for some time postpartum, particularly in lactating women. Thus it is possible that brain levels also are low during late pregnancy and the early postpartum period and that this maternal DHA depletion may contribute to postpartum depression.

In a recent study, published prevalence data for postpartum depression (n=14532 subjects in 41 studies) were compared to the DHA, EPA and AA content in mothers' milk and to seafood consumption rates in published reports from 23 countries. Higher concentrations of DHA in mothers' milk ( $p < 0.0001$ , n=16 countries) and greater seafood consumption ( $p < 0.0001$ , n=22 countries) predicted lower prevalence rates of postpartum depression. The AA and EPA content of mothers' milk were unrelated to postpartum depression prevalence (Hibbeln, 2002).

### **Bipolar Disorder**

All of the currently available mood-stabilizing drugs appear to inhibit neuronal signal transduction (or second messenger) systems, supporting the hypothesis that overactive cell-signaling pathways are involved in the pathological process underlying BP (Stoll et al., 1996). Biochemical studies have shown that high-dose therapy with omega-3 fatty acids leads to the incorporation of these compounds into the membrane phospholipids crucial for cell signaling (Medini et al., 1990; Sperling et al., 1993). The ingestion of large amounts of omega-3 fatty acids is associated with a general dampening of signal transduction pathways associated with phosphatidylinositol, AA, and other systems

(Sperling et al., 1993; Tappia et al., 1997). This mechanism is similar to the putative actions of lithium and valproate (Kinsella, 1990).

A recent study by Andrew Stoll et al. (1999) showed that dietary supplementation with DHA and EPA showed marked mood-stabilizing activity in BP. A 4-month, double-blind, placebo-controlled study compared 15 one-gram capsules of fish oil daily (containing 9.6 g/day omega-3 fatty acids) to an olive oil placebo, as an adjunct to usual treatment in 30 patients with BP. Participating subjects were men and women, 18 to 65 years old, who met DSM-IV criteria for BP (types I or II), and were free of other medical and psychiatric illnesses. Patients were required to have had at least one manic or hypomanic episode within the past year, in order to enhance the power of the study to detect a difference between the two treatment groups within the study period. Forty percent of the study cohort had rapid-cycling symptoms, defined as 4 or more mood episodes in the year before enrollment in the study. Subjects receiving other medications at entry continued to receive these medications at constant dosages (whether or not they were considered to be in the therapeutic range).

The patients receiving 15 g daily of fish oil had mild dose-related gastrointestinal distress (nausea and loose stools) as the primary complaint. Also, fishy breath was occasionally noted. The omega-3 fatty acid-treated group had a significantly longer period of remission than the placebo group ( $P = .002$ ); during the 4-month trial, 2 of 14 patients relapsed in the fish oil group while 9 of 16 relapsed in the placebo-treated group. Significant group differences in favor of fish oil were seen on the Hamilton depression scale, the Global Assessment Scale and the Clinical Global Impression. The authors concluded that omega-3 fatty acids were well tolerated and improved the short-term course of illness in this preliminary study of patients with BP (Stoll et al., 1999). These investigators are currently enrolling patients in a similar but better controlled and much larger trial paid for by the NIH.

### **Integrative Psychiatry: How to Do It - Some Case Examples**

So, how does one put the information presented in previous sections into practice? A compre-

hensive management program should include collaboration between the patient, the patient's family and the treating physician and/or psychiatrist. Ideally, an alternative practitioner will also be involved, and can assist in coordinating the efforts. While no one should treat themselves for BP (or any other major mental disorder), neither should they be a passive participant. Most practitioners (unless they specialize in children) will initially encounter BP in individuals who are already on medication. Treatment of BP requires healthcare professionals experienced in the management of severe mental disorders. Hospital admitting privileges should be available, since things can go wrong very quickly with these patients. Ideally, there will be a psychiatrist, experienced with BP, who is open to integrating some "natural" treatments in order to improve the care and enhance the quality of life of their patient.

As mentioned previously, a common situation is a person (call him MB) who has already been diagnosed with BP, is on two or three medications (e.g. lithium or valproic acid + fluoxetine, Prozac®), has side effects from all of them but is still not really well. While the crippling effects of severe depression are at bay, the symptom that often remains or recurs in MB is mild to moderate depression. How one approaches the healthcare practitioner depends on the present state of the patient. What may often happen is the psychiatrist will increase the dose of the antidepressant (in this case fluoxetine) or add a second antidepressant. This should be avoided, since it can initiate more problems including "rapid cycling". For MB, the simple addition of a fish oil supplement would be an appropriate beginning. A common scenario is that MB will begin responding to the fish oil with a relief of depressive and anxiety symptoms. Improvement may be seen as early as a few days and may be cumulative for several months.

Current consensus is that the 9.6 g of omega-3 used in the Stoll study is more than is needed. Thus, one could aim for a total of 3-5 g of omega-3 (EPA + DHA) per day, in divided doses to reduce GI upset. Stomach upset and reflux are also minimized by taking after meals. Some people prefer to take the entire dose just before bed. If this works for them, fine. There is some anecdotal evidence that DHA may be better for a

calming or antimanic effect and EPA better for an uplifting or antidepressant effect. There are formulations available that favor one or the other omega-3, and these can be tried. But be careful – both concentrated EPA formulations and flaxseed oil have been associated with inducing hypomania or mania. This has not been reported for plain fish oil which is usually a ratio of about 3:2 EPA to DHA. On the other hand, DHA has been found in one study and in anecdotal use to be ineffective in depression.

At some point, the patient, the family, and the treating physician will be convinced that the improvement is real and will be agreeable to slowly reduce the other medications that are causing the most side effects. A reduction of around 25% per week is usually manageable. Don't ever withdraw medication rapidly since relapse is much more likely. A withdrawal syndrome can also be initiated with too rapid discontinuation of many medications. This should be avoided if possible since it can be very unpleasant and may itself resemble symptoms of psychiatric illness, making it much more difficult to manage the treatment. It is advisable to change only one thing at a time, whenever possible. In this way you have more confidence that any improvement or worsening of symptoms is related to what was most recently added or deleted.

The next patient is similar to MB, but instead of depression, has occasional hypomanic symptoms or perhaps even a full episode of mania. This person (SA) is probably on lithium, valproic acid and perhaps an antipsychotic. Side effects are causing such cognitive impairment that work or school may be impossible. She has gained 50 pounds since starting medications 2 years ago. Again, a fish oil addition may be very helpful, and can do no harm. It can be added to the existing medications. Flaxseed oil and EPA weighted formulations should probably be avoided by SA due to reasons mentioned above (too stimulating). Improvement in symptoms may be more difficult to pin down since she has been having episodes only once every 6 months. However, as patients begin to improve they may become even more sedated from the ongoing medication. This is actually one of the signs of improvement since patients become more sensitive to the side effects (such as cognitive

impairment) as they get better. At some point, all will agree that the improvement is real and the next steps can be planned. This case is trickier since a manic episode can be so destructive for all concerned and must be avoided. Any medication reductions should be done very slowly and with close observation. If SA is not currently stable, but instead is escalating into a manic episode, the treating physician may also wish to consider adding verapamil to the omega-3. This can be done with an initial dose of 120 mg per day. Be aware of possible lowering of blood pressure, resulting in dizziness, especially on standing. This dose can be gradually increased up to a maximum of 480 mg per day. Addition of verapamil must be done very carefully if SA is on carbamazepine, since metabolism of the anticonvulsant is reduced by verapamil and toxic blood levels could result.

A final patient, KW, has been on lithium and has not had a BP episode for 3 years however, she is now considering having a child. Since complete withdrawal of lithium might result in a relapse, what else can be done? Depending on her history, this patient is a good candidate for fish oil or fish oil plus verapamil. If she has a primary history of depression, then omega-3 alone may suffice. Once maximum doses of omega-3 are seen to be tolerated well for a few weeks, lithium can be withdrawn at a maximum of 25% per week. Small amounts of flax oil (up to 1 tablespoon per day) could be added if any hint of depression appears. Verapamil could be added if depression persists, or if her prior history was characterized by mania in addition to depression.

While there are many examples of people you know who do not fit into any of these categories, the principles still apply. They include: 1) don't treat yourself; 2) fish oil is safe and effective for a broad variety of mental or emotional disorders; 3) change only one parameter at a time so you know what to do if something goes wrong; and 4) reduce medications gradually – 25% per week usually is safe. Herbal preparations (e.g. St. Johns Wort, kava, skullcap) can be useful for relief of minor symptoms of depression, anxiety, insomnia, etc. that often accompany major mental disorders. Use an extra measure of caution when providing them to BP patients, however, since things can go wrong very quickly.

An understanding and supportive family is critical to help with monitoring medication changes and prevent small mood changes from becoming big ones. Educate them and enlist their help.

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